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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/197,056	11/20/1998	STEPHEN JAMES RUSSELL	3789/77553	9864

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/19/2002

27

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/197,056	Russell et al.
Examiner	**Art Unit**
Michael C. Wilson	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 23, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-40* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-23-02, paper number 25, has been entered.

Applicant's arguments filed 9-23-02, paper number 26, have been fully considered but they are not persuasive. Claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18-20 have been canceled. Claims 21-40 have been added and are under consideration in the instant office action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in the United Kingdom on 9-6-97 and 11-7-97 (9718872.6 and 9723448.8). The certified

copy of the applications were received 3-14-02 and have been entered into the file (paper number 19).

Claim Rejections - 35 USC § 112

1. Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have not pointed to support for specific limitations found in claims 21-40. Applicants merely state the claims are supported, for example, on pg 9, lines 7-19, which teaches "delay[ing] expression of the immunogenic polypeptide following introduction of the cell expressing the polypeptide into the mammal, in a preferred embodiment, prior to introduction of the cell into the mammal the expression of the immunogenic polypeptide is substantially inhibited *in vitro*, and expression of the immunogenic polypeptide reaches a maximum level in the mammal after a delay." However, the sentence is unclear. How does one delay expression after the cell is introduced into a mammal? How does the phrase "prior to introduction of the cell... expression... is substantially inhibited *in vitro*, and expression... reaches a maximum level in the mammal after a delay" relate to the delay? Is "a delay" referring to inhibiting expression *in vitro* or is it some other delay that occurs? Pg 9, lines 7-19, does not correlate to the claims because it requires

inhibiting expression of the polypeptide *in vitro* prior to administering the cell into the mammal, which is not a step in the claims.

A cell "not maximally expressing said polypeptide during said introducing step" (claim 21) is new matter. Pg 9, lines 7-19, supports inhibiting expression *in vitro* and increasing expression after introducing the cell into a mammal. Cells "not maximally expressing" a protein prior to being administered (claim 21) are broader in scope than cells having inhibited expression *in vitro* prior to being administered (pg 9) because cells in the claim are not *in vitro* and because the metes and bounds of maximal expression are unclear. In addition, the specification as written encompasses the possibility that maximum expression occurs during the introducing step. It cannot be determined how "after a delay" on pg 9, line 11, of the specification defines the timing of the "introducing" and the "expression."

The phrase "wherein said mammal exhibits an immune response against said polypeptide prior to said introducing step" (claim 21) is new matter. Support for exhibiting an immune response prior to "introducing" cannot be found.

The phrase delaying "enhanced" expression is new matter (claim 21). Support for altering the concentration of inducing agent such that "enhanced" expression is induced has not been provided and cannot be found. It appears that the agent causes an increase in expression upon being administered. Expression is "enhanced" as compared to what?

Claims 26 and 27 is new matter. Support has not been provided and cannot be found.

A cell autologous to a human (claims 29 and 35) or human cells in general comprising the vector as claimed is new matter. Support is not found on pg 17, lines 6-8, which only disclose the genus of mammal, and cannot be found elsewhere in the specification as originally filed.

The phrase "wherein said human exhibits an immune response against said polypeptide" (claim 29 and 35) is new matter. Support has not been provided and cannot be found. While pg 17, lines 6-8 support cells autologous to a mammal, wherein said cells comprise a vector encoding a protein, support for the cells being autologous to a mammal exhibiting an immune response against the protein cannot be found.

Claim 32 and 38 are new matter. Support for cells expressing a protein, wherein the cells were isolated from a human having an antibody response against the protein has not been provided and cannot be found.

Failure to identify where support for future newly added limitations are found in the disclosure as originally filed will be considered non-responsive. Support should be by page and line number and should be correlated to a specific limitation. See 37 CFR 1.121(b)(2)(iii).

The rejection of claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18-20 under 35 U.S.C. 112, first paragraph, has been withdrawn because the claims have been canceled.

2. Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising a) transfecting a cell with a nucleic acid sequence encoding a protein operably linked to a tetracycline regulatable promoter *in vitro*, and b)

increasing expression of the protein using tetracycline *in vitro*, does not reasonably provide enablement for administering the cells to a mammal that has had an immune response against the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 21-28 require increasing expression of a protein in a cell after it has been administered into a mammal, wherein said mammal has had an immune response against said protein prior to administering the cells. Claims 29-34 require human cells comprising a vector comprising a nucleic acid sequence encoding a protein operably linked to a regulatable promoter, wherein said cells are autologous to a human that exhibits an immune response against said polypeptide. Claims 35-40 require a composition comprising the cells and a physiologically acceptable diluent. The only disclosed purpose for such methods, cells and compositions are for therapy.

However, the combination of vector, promoter, level of expression, target tissue, dosage and route of administration required to obtain a therapeutic effect using gene therapy were unpredictable at the time of filing (Ross of record, 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1786, col. 1, para. 2, pg 1786, col. 1, para. 2; Verma of record, Sept. 18, 1997, Nature, Vol. 389, pg 239-242, see pg 239, 3rd col., line 10, pg 239, col. 1, line 16) for reasons of record.

To further support the unpredictability of the combination of elements required to obtain a therapeutic effect using gene therapy, the following references are provided: Miller (1995,

FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The specification demonstrates transfecting Jurkat cells with a vector encoding a chimeric T-cell receptor (TCR) operably linked to the tetracycline operator and encoding tTA. The expression of the TCR is increased by decreasing the concentration of tetracycline *in vitro* (page 31). The specification does not teach administering cells to a mammal, regulating protein expression in a mammal, obtaining a therapeutic effect, how to use cells expressing TCR *in vivo*, how to increase expression of the TCR after the cells have been administered to a mammal, why

such cells would be administered to a mammal having an immune response against the TCR. The specification does not correlate the cells expressing TCR to cells expressing a protein that could be therapeutic in a mammal that has had an immune response to the protein. Overall, the specification does not overcome the unpredictability in the art by teaching the level of expression, route of administration, vector, promoter or cells required to obtain a therapeutic effect. Given the guidance provided in the specification taken with the unpredictability in the art, it would have required one of skill in the art undue experimentation to determine the parameters required to obtain a therapeutic effect using the method claimed.

Applicants argue one of skill could have made the cell, administered it to a mammal and increased expression of the protein after administering the cell to the mammal (pg 6 of arguments). "This is especially true given the many publications describing the use of regulatable promoters to regulate polypeptide expression. See, e.g., Applicants' specification at page 10, lines 9-12. Thus, Applicants' specification fully enables new claims 21-28." Applicants argument is not persuasive. The specification does not provide adequate guidance to obtain a therapeutic effect by increasing expression of the protein *in vivo* for reasons cited above. Merely increasing expression of a protein in the absence of therapeutic effect does not have a disclosed use in a mammal having an immune response to the protein prior to administering the cell. In addition, the specification does not teach how to regulate protein expression *in vivo*. Finally, pg 10, lines 9-12, does not enable administering the cell to a mammal or increasing expression of the protein *in vivo*. Pg 10, lines 9-12 merely describes "suitable drug-regulatable promoters." The specification does

not provide adequate guidance to regulate protein expression *in vivo* or to determine the combination of elements required to use the method claimed to obtain a therapeutic effect.

3. Claims 21-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of what applicants consider "enhanced expression" (claim 21 27) cannot be envisioned. Expression is "enhanced" as compared to what? What are the metes and bounds of "enhanced" compared to normal expression? How is "enhanced" expression delayed? The specification does not provide a definition of "enhanced" expression and the art at the time of filing did not define "enhanced" expression. Therefore, the metes and bounds of "delaying enhanced expression" and "such that enhanced expression" cannot be determined.

The phrase "to a time following said introduction" (claim 21) is unclear. Does the phrase correlate to "delaying" or "introducing"? If it relates to delaying, how does "delaying... ...expression to a time following said introduction" further limit the claim which already requires obtaining "enhanced expression... ...after said introducing step"? Is expression increased after the cells are introduced? If the claim merely requires an increase in expression after the cells are introduced into the mammal, such a step should be clearly set forth. "Enhancing" and "delaying" expression together is confusing.

Claims 21-28 are indefinite because it is unclear whether the phrase "is regulated by an inducing agent" (claim 21) means the inducing agent is administered and the step of "regulating"

occurs, or if the phrase merely means that the promoter is capable of being regulated by an inducing agent. As such, it cannot be determined if administering the inducing agent is required in the claim.

The metes and bounds of cells "not maximally expressing said polypeptide during said introducing step" (claim 21) cannot be envisioned. The specification does not define "maximal" expression and the term is relative in the art. Therefore, the metes and bounds of "maximal" expression in a cell cannot be determined. It cannot be determined if the polypeptide is expressed in the cell during the introducing step. As such, the metes and bounds of the cells being introduced into the are not clearly set forth.

The phrase "wherein said mammal exhibits an immune response against said polypeptide prior to said introducing step" is unclear. "Said polypeptide" refers to either the polypeptide in the vector (a) or the polypeptide expressed by a cell in the preamble. But the mammal cannot induce an immune response against the polypeptide in the vector or expressed by the cell prior to the "introducing" step because the cell comprising the vector has not been introduced. If applicants intend the "introducing" step to be limited to "introducing a cell into a mammal exhibiting an immune response against a polypeptide," such a limitation should be clearly set forth.

The phrase "altering the concentration of said inducing agent to which the cell is exposed" (claim 21) is indefinite because the cells are not exposed to the inducing agent in the first place.

Therefore, the concentration cannot be "altered" as claimed and the "concentration... ...to which the cell is exposed" lacks antecedent basis.

It is unclear whether the limitation of claim 24 further limits the immune response of the mammal prior to "introducing" or is an additional step requiring a reacting circulating antibodies and the polypeptide prior to "introducing". It cannot be determined if the circulating antibodies further limit the "immune response" in the mammal of claim 21 or if the circulating antibodies reacting with the polypeptide is an additional step.

It is unclear how the limitation of claim 26 further limits claim 21. It is unclear whether "exposing said cell" in claim 26 means exposing the cell in the preamble or in step (a) to tetracycline or tetracycline analog. As such it cannot be determined if the limitation of claim 26 further limits "is regulated by an inducing agent" in claim 21 or is a separate step. Therefore, the metes and bounds of the steps encompassed by the claim are not clearly set forth.

It is unclear how claim 27 further limits claim 25 or 21. Is maximal expression obtained two days after "introducing" or is "enhanced expression" "induced" two days after "introducing"? The step is not clearly set forth or correlated to claim 21.

Claim Rejections - 35 USC § 102

The rejection of claims 1 and 18 under 35 U.S.C. 102(b) as being anticipated by Shockett (July 1995, PNAS, USA, Vol. 92, pages 6522-6526) has been withdrawn because the claims have been canceled.

The rejection of claims 14 and 16 under 35 U.S.C. 102(a) as being anticipated by Cooke (Feb. 1997, J. General Virol., Vol. 78, pages 381-392) has been withdrawn because the claims have been canceled.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless - . .
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 29-40 are rejected under 35 U.S.C. 102(a) as being anticipated by Cooke of record (Feb. 1997, J. General Virol., Vol. 78, pages 381-392).

Cooke taught human T cell lines with a vector encoding *nef* operably linked to a CMV/tetracycline operator promoter and a vector encoding tTA (page 382, col. 2, first and second full paragraphs; page 383, Fig. 1 and legend of Fig. 1). *Nef* is considered an immunogenic polypeptide because it is a viral protein that is recognized by mammals as foreign. T cells are "leukocytes" as claimed. The T-cells are "autologous" to the human from whom they were isolated. The phrase "wherein said human exhibits an immune response against said polypeptide" does not bear patentable weight because it does not alter the function of the cells claimed. A cell isolated from a human exhibiting an immune response against the protein has the same function as

a cell isolated from a human not exhibiting an immune response against the protein. Therefore, the phrase does not distinguish the cells claimed from those taught by Knaus. Therefore, Cooke anticipates the claims.

5. Claims 29-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Knaus (July 1996, Mol. Cell. Biology, Vol. 16, pg 3480-3489).

Knaus taught Mac-1 and Mac2A cells comprising a retroviral vector encoding wild-type TβRII or mutant D404G-TβRII operably linked to a tetracycline-regulatable promoter (pg 3481, Materials and Methods, "Retroviral vectors," last sentence, "Retroviral infection for the generation of stable Mac-2A cell lines expressing wt TβRII," "Retroviral infection for the generation of stable Mac-1 cell lines expressing wt TβRII;" Results, "Absence of surface TβRII and TβRI in Mac-2A...," first para., 2nd and 4th sentences, 2nd para., first two sentences. Mac-1 and Mac2A are human T-cell lines (pg 3481, col. 2, Results, "Absence... ...in Mac-2A, a... ...T-cell lymphoma line;"). Mac-1 and Mac-2A are "autologous" to the human from whom they were isolated. The phrase "wherein said human exhibits an immune response against said polypeptide" does not bear patentable weight because it does not alter the function of the cells claimed. A cell isolated from a human exhibiting an immune response against the protein has the same function as a cell isolated from a human not exhibiting an immune response against the protein. Therefore, the phrase does not distinguish the cells claimed from those taught by Knaus. Assuming for argument's sake, the phrase "wherein said human exhibits an immune response against said polypeptide" bears patentable weight and gives a function to the cells, Mac-1 cells anticipate the

claims. Mac-1 was derived from a tumor that spontaneously regressed (pg 3481, col. 2, Results, first para., second sentence). Therefore, the patient induced an immune response against TβRII causing regression of the tumor. The media used by Knaus to culture Mac-1 and Mac-2A is a "pharmacologically acceptable diluent" (claims 35-40).

Claim Rejections - 35 USC § 103

The rejection of claim 18 under 35 U.S.C. 103(a) as being unpatentable over Hoffmann of record (May 1996, PNAS, Vol. 93, pages 5185-5190) has been withdrawn because the claim has been canceled.

Claims 21-28 appear to be free of the prior art of record because the prior art of record did not teach a method comprising i) administering cells to a mammal, said cells comprising a nucleic acid sequence encoding a protein operably linked to an inducible promoter, wherein said mammal exhibits an immune response against said protein prior to administering the cells, and ii) increasing expression of said protein using an inducing agent after administering the cells.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

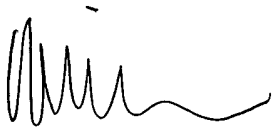
Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER